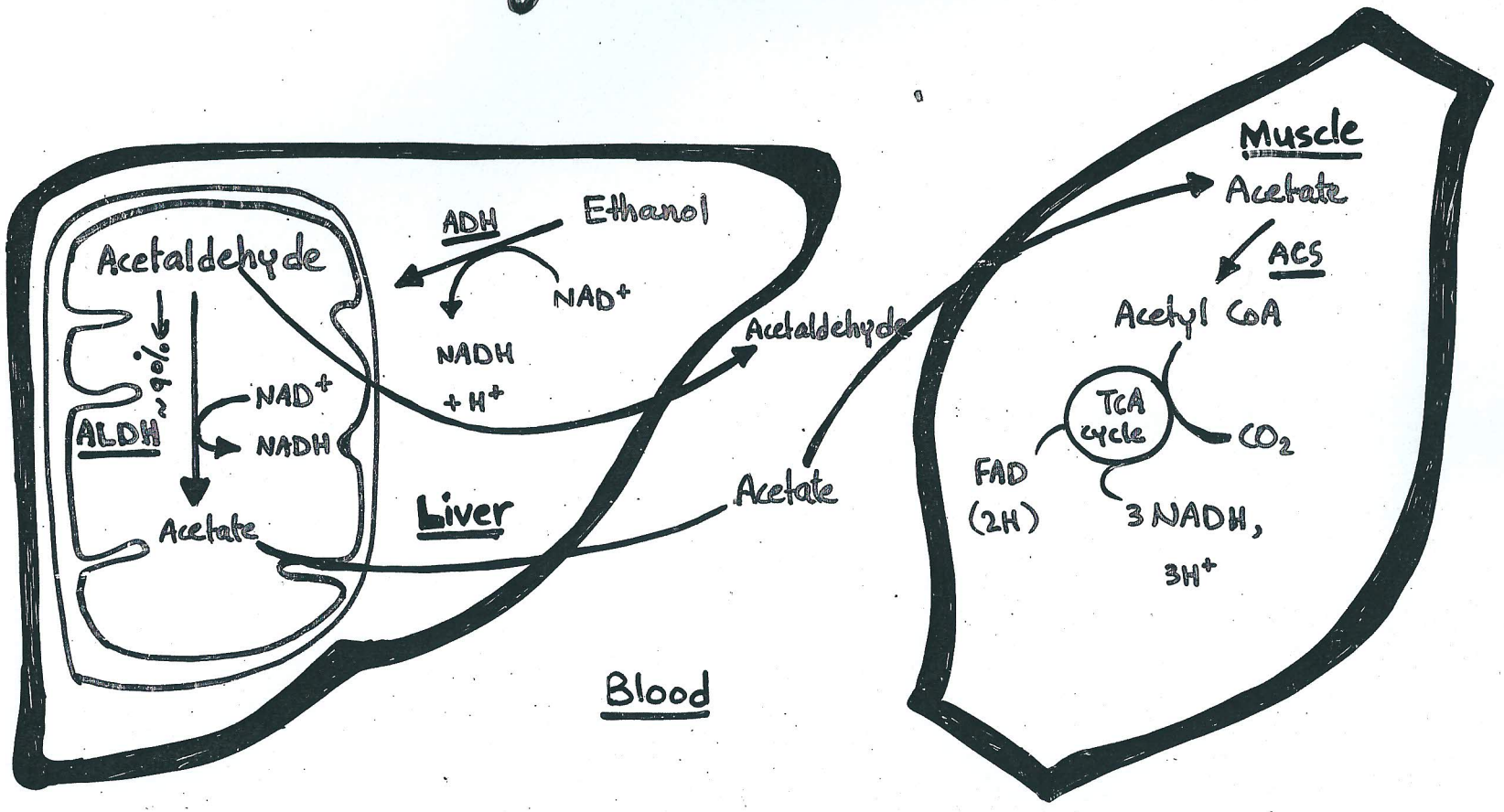
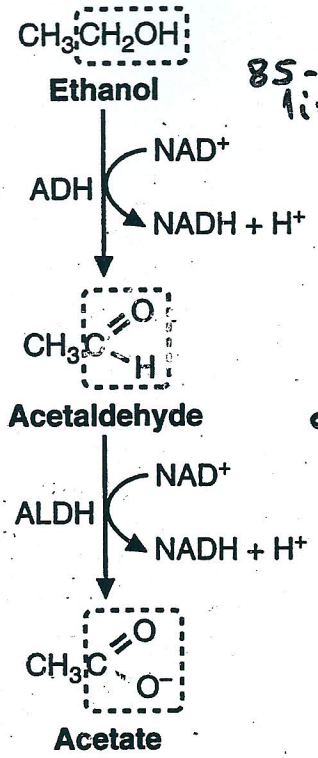
Overall Metabolism of Alcohol and Acetate



ADH: Alcohol dehydrogenase
ALDH: Acetaldehyde dehydrogenase
ACS: Acetyl CoA synthetase

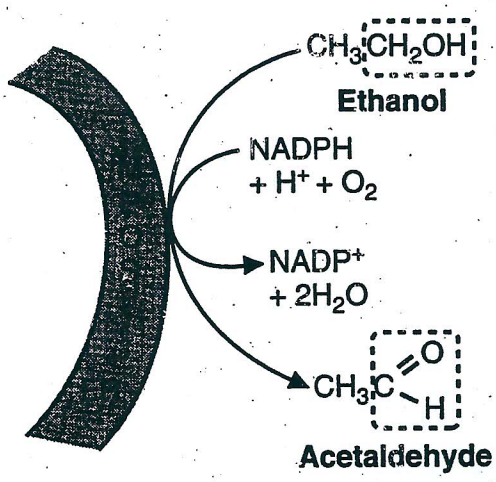


85-90% metabolized in liver cytoplasm

2-10% excreted by lung + kidneys.

about 90% of acetaldehyde ↓ in liver mitochondria

Fig. 25.2. The pathway of ethanol metabolism (ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase).



- Accounts for 10-20% Oxn of EtOH
- Has a high Km for EtOH

Fig. 25.3. The reaction catalyzed by MEOS (which includes CYP2E1) in the endoplasmic reticulum.

ACS Cytosolic enzy in muscles & other tissues → Acetyl CoA for cholesterol & FA synthesis

Mitochondrial ACS is in heart & skeletal muscle → TCA

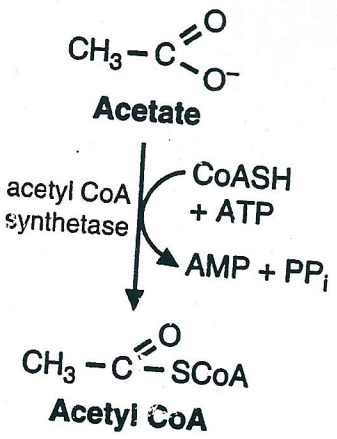


Fig. 25.4. The activation of acetate to acetyl CoA

CYP 2E1 is part of the superfamily of Cyt P450 enzymes

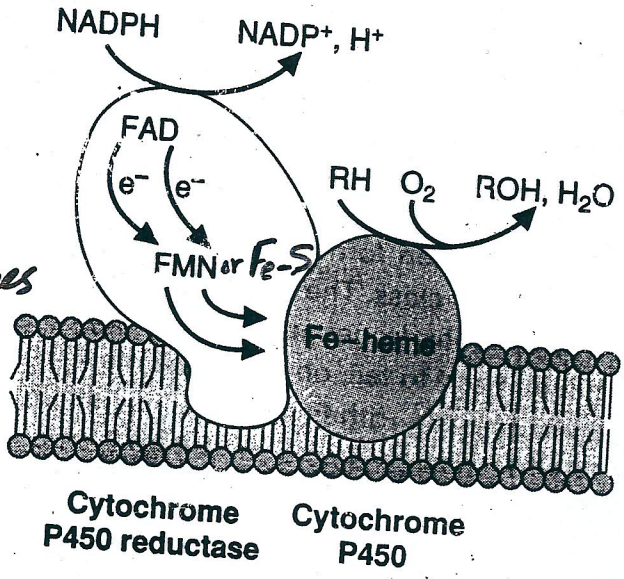


Fig. 25.5. General structure of cytochrome P450 enzymes. O_2 binds to the P450 Fe-heme in the active site and is activated to a reactive form by accepting electrons. The electrons are donated by the cytochrome P450 reductase, which contains an FAD plus an FMN or Fe-S center to facilitate the transfer of single electrons from NADPH to O_2. The P450 enzymes involved in steroidogenesis have a somewhat different structure. For CYP2E1, RH is ethanol (CH_3CH_2OH) and ROH is acetaldehyde (CH_3COH).

Metabolism of Ethanol

***Ethanol** is a **dietary fuel** that is metabolized to acetate principally in the liver, with the generation of NADH. The principal route for metabolism of ethanol is through hepatic **alcohol dehydrogenases**, which oxidize ethanol to **acetaldehyde** in the cytosol (Fig. 25.1). Acetaldehyde is further oxidized by **acetaldehyde dehydrogenases** to **acetate**, principally **in mitochondria**. Acetaldehyde, which is toxic, also may enter the blood. **NADH** produced by these reactions is used for adenosine triphosphate (ATP) generation through oxidative phosphorylation. Most of the acetate enters the blood and is taken up by skeletal muscles and other tissues, where it is activated to **acetyl CoA** and is oxidized in the TCA cycle.*

*Approximately 10 to 20% of ingested ethanol is oxidized through a microsomal oxidizing system (**MEOS**), comprising **cytochrome P450** enzymes in the endoplasmic reticulum (especially **CYP2E1**). CYP2E1 has a high K_m for ethanol and is inducible by ethanol. Therefore, the proportion of ethanol metabolized through this route is greater at high ethanol concentrations, and greater after chronic consumption of ethanol.*

Acute effects *of alcohol ingestion arise principally from the generation of* $NADH$, *which greatly increases the* ***NADH/NAD$^+$*** *ratio of the liver. As a consequence,* ***fatty acid oxidation is inhibited****, and* ***ketogenesis*** *may occur. The elevated* ***NADH/NAD$^+$*** *ratio may also cause* ***lactic acidosis*** *and inhibit* ***gluconeogenesis.***

Ethanol metabolism may result in ***alchohol-induced liver disease****, including* ***hepatic steatosis*** *(fatty liver),* ***alcohol-induced hepatitis****, and* ***cirrhosis****. The principal toxic products of ethanol metabolism include* ***acetaldehyde*** *and* ***free radicals.*** *Acetaldehyde forms* ***adducts*** *with proteins and other compounds. The* ***hydroxyethyl radical*** *produced by MEOS and other radicals produced during*

inflammation cause irreversible damage to the liver. Many other tissues are adversely affected by ethanol, acetaldehyde, or by the consequences of ***hepatic dysmetabolism*** *and injury.* ***Genetic polymorphisms*** *in the enzymes of ethanol metabolism may be responsible for individual variations in the development of alcoholism or the development of liver cirrhosis.*